ABSTRACT

The invention overcomes the deficiencies of the prior art by providing a rapid approach for isolating binding proteins capable of binding small molecules and peptides *via* "display-less" library screening. In the technique, libraries of candidate binding proteins, such as antibody sequences, are expressed in soluble form in the periplasmic space of gram negative bacteria, such as *Escherichia coli*, and are mixed with a labeled ligand. In clones expressing recombinant polypeptides with affinity for the ligand, the concentration of the labeled ligand bound to the binding protein is increased and allows the cells to be isolated from the rest of the library. Where fluorescent labeling of the target ligand is used, cells may be isolated by fluorescence activated cell sorting (FACS). The approach is more rapid than prior art methods and avoids problems associated with the surface-expression of ligand fusion proteins employed with phage display.